

(CPO) exposure, especially if combined with lower plasma levels of PON1. We examined the neurodevelopmental effects associated with low-level chronic exposure of mice to CPO during postnatal development. PON1 knockout (PON1<sup>-/-</sup>), wild-type (WT) and humanized tgHuPON1Q192 and tgHuPON1R192 transgenic mice were used to determine whether PON1 status modulated the effects of CPO exposure on gene expression in the cerebellum. Neonatal mice were exposed to CPO (0, 0.15, 0.18, 0.25, 0.35 or 0.50 mg/kg/d) daily from PND4-21. Chronic CPO exposure resulted in dose-related decreases in brain acetylcholinesterase activity by PND22 in PON1<sup>-/-</sup> and tgHuPON1Q192 mice, but not in WT or tgHuPON1R192 mice. Gene expression was measured on PND22 using Affymetrix Mouse Genome microarrays. All four genotypes exposed to CPO (0.35 or 0.50 mg/kg/d) showed significant differences in gene expression compared with controls. Pathway analysis and Gene Set Analysis revealed multiple pathways and gene sets affected by CPO exposure, including genes involved in mitochondrial dysfunction, oxidative stress, neurotransmission, and nervous system development. Changes in gene expression were modulated differentially by the two Q192R alloforms, with the most overlap in significantly-enriched gene sets occurring between the tgHuPON1Q192 and PON1<sup>-/-</sup> mice. These findings indicate that neonatal CPO exposure is associated with wide-ranging effects on gene expression in the brain, and that PON1 status can modulate these effects, even when PON1 levels are low during early development. Supported by ES11387, ES09601/EPA-R826886, ES09883, ES04696, ES07033.

### **PS 1327 CHLORPYRIFOS AND CHLORPYRIFOS OXON ALTER RYANODINE RECEPTOR FUNCTION.**

Y. Niknam, A. Ghogha, P. Lein and I. Pessah. Molecular Biosciences, School of Veterinary Medicine, UC Davis, Davis, CA.

An accepted mechanism of organophosphorus (OP) insecticide-induced neurotoxicity is inhibition of acetylcholinesterase (AChE), the enzyme that hydrolyzes the neurotransmitter acetylcholine. However, several neurotoxic actions of OPs cannot be directly attributed to AChE inhibition. In a screen of 250 environmental chemicals, chlorpyrifos (CPF), a widely used OP, was identified as a potent modulator of type 1 and type 2 ryanodine receptors (RyR1 and RyR2, respectively), broadly expressed ion channels that regulate the release of Ca<sup>2+</sup> from endoplasmic/sarcoplasmic intracellular calcium stores. We further investigated the mechanism and specificity by which CPF, its major bioactive metabolite chlorpyrifos oxon (CPFO), and the predominant breakdown product trichloro-2-pyridinol (TCP) influence RyR1 and RyR2 function using [<sup>3</sup>H]ryanodine receptor binding analysis, western blotting to detect RyR phosphorylation and electrical recordings of primary sympathetic neurons cultured on multi-electrode arrays (MEAs). Radioligand binding assays performed at 37°C indicated a non-monotonic concentration-effect relationship with low μM concentrations of CPF and CPFO maximally enhancing RyR1 occupancy by 2.4- and 7.5-fold, respectively. CPF and CPFO showed significantly less activation of RyR2 at 37°C (1.3- and 3-fold of control), whereas 1μM CPF was more efficacious toward RyR2 at 25°C (3.3-fold of control). TCP showed negligible activity towards RyR1 and RyR2 under either experimental condition. Western blotting of microsomes treated with <20μM CPF did not show differences in RyR1 phosphorylation at serine-2844 compared to solvent controls. Acute exposure to CPF and CPFO, but not TCP, increased spontaneously activity in cultured sympathetic neurons (2, 3 and 4.5 fold of control at 1, 10 and 100nM CPF; 3 and 3.3 fold of control at 1 and 10nM for CPFO). These data identify RyRs as a sensitive target of CPF and CPFO that may contribute to non-AChE-mediated OP neurotoxicity. Sponsored by NIH (P42 ES04699 to INP and R01 ES16308 to WKA and PJL).

### **PS 1328 OCCUPATIONAL PESTICIDE EXPOSURE AND NEUROBEHAVIORAL DEFICITS IN AN ADOLESCENT POPULATION.**

D. Rohlman<sup>1</sup>, A. Ismail<sup>2</sup>, J. R. Olson<sup>3</sup>, O. Hendy<sup>3</sup> and G. Abdel Rasoul<sup>3</sup>. <sup>1</sup>CROET, Oregon Health & Science University, Portland, OR, <sup>2</sup>Menoufia University, Shebin Elkom, Egypt and <sup>3</sup>State University of New York at Buffalo, Buffalo, NY.

Agricultural workers, both adults and adolescents, are at risk for many occupational hazards including workplace injuries and exposure to pesticides. Pesticides are thought to pose a considerably higher risk to children than to adults, yet little is known about the extent or magnitude of health problems related to occupational exposure to pesticides in children and adolescents. Experimental animal studies indicate that the developing brain is more susceptible to the neurotoxic effects of organophosphorus (OP) pesticides than the adult brain, and low-level exposures to OP pesticides cause significant neurobehavioral deficits in animal research. Adolescents in Egypt are hired seasonally to work as pesticide applicators for the

cotton crop. The pesticide application to the cotton crop is highly regulated and standardized across Egypt, and has been limited primarily to organophosphorus pesticides, generally chlorpyrifos, in recent years. Adolescent applicators and Controls completed a battery of neurobehavioral tests, an occupational and symptoms questionnaire and a medical exam. Blood and urine samples were collected to evaluate biomarkers of OP exposure. Thirty two percent of Applicators had plasma butyrylcholinesterase (BuChE) activity lower than normative data, compared to 5% of Controls. Applicators also had significantly higher levels of trichloro-2-pyridinol (TCPy), a chlorpyrifos-specific metabolite in their urine ( $p < 0.05$ ) and decreased neurobehavioral performance compared to Controls. Applicators performed worse on 10 out of 12 of the neurobehavioral tests, significant differences ( $p < 0.05$ ) were found on Match-to-Sample, Symbol-Digit, Finger Tapping, and Block Design. Work practice questionnaires indicate limited use of personal protective equipment. This study provides data to characterize exposure and identifies deficits in an adolescent population occupationally exposed to pesticides. (NIH R01 ES016308)

### **PS 1329 BEHAVIORAL DEFICITS IN EGYPTIAN APPLICATION TEAMS WITH CHRONIC ORGANOPHOSPHORUS PESTICIDE EXPOSURES.**

W. K. Anger<sup>1</sup>, F. M. Farahat<sup>2</sup>, P. J. Lein<sup>3</sup>, J. R. Olson<sup>4</sup> and D. S. Rohlman<sup>1</sup>.

<sup>1</sup>CROET, Oregon Health & Science University, Portland, OR, <sup>2</sup>Menoufia University, Shebin Elkom, Menoufia, Egypt, <sup>3</sup>University of California, Davis, CA and <sup>4</sup>State University of New York at Buffalo, Buffalo, NY.

Chronic exposure to organophosphorus pesticides (OPs) has been consistently associated with deficits on neurobehavioral tests in workers using pesticides as compared to controls in most of the 24 published studies of these working populations. While years of applying OPs have correlated with effect in 3 studies, a dose-response relationship has not been identified, leading some to doubt the association. We identified a population of pesticide applicators in Egypt primarily exposed to one OP, chlorpyrifos, with limited exposure to other pesticides. Application teams are composed of engineers (who do not typically enter the fields during applications), technicians (who walk side-by-side with the applicators in the fields), and applicators (highest exposures) who are typically seasonal workers. A chlorpyrifos-specific metabolite measured in urine confirmed the pattern of lower to higher exposures across these job categories in this population. Trailmaking, a timed test which requires a broad range of cognitive capabilities, was administered to 60 technicians, 64 engineers, and 20 controls who did not work in agriculture (very low exposures) 3 times during the OP application season and again 1.5 months after applications had ended. Time to complete Trailmaking B improved in each group with a mean overall improvement of 42 secs. A consistent dose-response relationship was seen in test performance speed across all 3 sessions: Controls had the best performance, engineers had slower performance (mean 28 sec slower than controls), and technicians (highest-exposed) had the slowest performance (mean 44 sec slower than controls). When performance was again tested at 1.5 months after applications ended, technicians were a mean of 21 sec slower than engineers, suggesting that the differences between the groups were persistent. Sponsored by NIH R01 ES016308 to WKA and PJL.

### **PS 1330 BIOMARKERS OF NEUROTOXICITY IN A RAT MODEL OF OCCUPATIONAL CHLORPYRIFOS (CPF) EXPOSURE.**

N. Hussainzada<sup>1,2</sup>, D. Jackson<sup>2</sup>, D. Bruun<sup>3</sup>, D. Milatovic<sup>4</sup>, J. Lewis<sup>2</sup>, C. Banks<sup>3</sup>, M. Aschner<sup>4</sup>, R. Browne<sup>5</sup>, J. R. Olson<sup>5</sup> and P. Lein<sup>3</sup>. <sup>1</sup>Orise Postdoctoral Fellow, Fort Detrick, MD, <sup>2</sup>USACE HR, U.S. Army, Fort Detrick, MD, <sup>3</sup>University of California, Davis, CA, <sup>4</sup>Vanderbilt University, Nashville, TN and <sup>5</sup>State University of New York at Buffalo, Buffalo, NY.

Identifying individuals at risk for cognitive deficits from repeated low-dose exposure to organophosphorous pesticides (OP) is limited by lack of predictive biomarkers. To address this, we developed a rat model of OP-induced neurotoxicity based on CPF exposure patterns in Egyptian pesticide applicators. Adult male Long Evans rats exposed to CPF (3 or 10 mg/kg/d, s.c.) exhibit significant dose-dependent deficits in Pavlovian fear conditioning at 21 but not 4 or 10 days. Tissues from these animals were used for transcriptomic profiling of the hippocampus in parallel with quantification of peripheral and central biomarkers of CPF exposure, inflammation and oxidative stress. Hippocampal genes differentially regulated by CPF were significantly enriched in biological pathways relevant to synaptic plasticity, cell-to-cell signaling, cell death, inflammation and oxidative stress. CPF also altered